

True and Apparent Hypertension Resistance: Epidemiology and Clinical Effects

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Introduction

With increased efforts to improve BP control rates and the emergence of device-based therapies for hypertension, resistive hypertension; defined as Blood Pressure (BP) remaining above goal despite the use of three or more antihypertensive medications at maximally tolerated doses (one of which should ideally be a diuretic) has received more attention. Patients with true resistant hypertension, controlled resistant hypertension, and pseudo-resistant hypertension make up this classically defined resistant group. The term "apparent" resistant hypertension has been used to identify "apparent" lack of control on 3 medications in studies where pseudo-resistant hypertension cannot be excluded (for example, 24-hour ambulatory BP was not obtained). The prevalence of resistant hypertension has recently been reported in large, well-designed studies. The prevalence of resistant hypertension is 14.8% of treated hypertensive patients and 12.5% of all hypertensives, based on prevalence data from these studies and others in North America and Europe with a combined sample size of more than 600,000 hypertensive participants. However, in terms of identifying risk and estimating benefit from newer therapies like renal denervation, the prevalence of true resistant hypertension; defined as uncontrolled by office and 24-hour ambulatory BP monitoring with confirmed medication adherence; may be more significant. In patients with resistant hypertension, rates of cardiovascular events and mortality follow mean 24-hour ambulatory BPs, with true resistant hypertension representing the highest risk. In large trials, the prevalence of true resistant hypertension has not been directly measured; however, the combined results of a number of smaller studies suggest that true resistant hypertension is present in half of the office-controlled resistant hypertensive patients. Uncontrolled resistant hypertension is prevalent in 10.1% of treated hypertensive patients and 7.9% of all hypertensive patients, according to our pooled analysis. Understanding the epidemiology and clinical implications of these two forms of hypertension resistance is critical for tailoring effective treatment strategies and improving patient outcomes. True resistant hypertension is closely linked to significant cardiovascular risks and warrants aggressive intervention, while apparent resistance can often be mitigated by addressing modifiable factors. Exploring the interplay between these conditions provides a comprehensive lens through which clinicians can better understand their prevalence, underlying mechanisms, and long-term effects on health.

Description

In the beginning, the term "resistant hypertension" was used to identify a group of high-risk patients who might benefit from specialized care, such as the examination and treatment of secondary hypertension causes. An American Heart Association (AHA) scientific statement established the definition as a BP that remains above target despite optimal doses of three different classes

of antihypertensive medication, one of which should ideally be a diuretic. By extension, a patient remains resistant if a fourth antihypertensive medication is added to maintain BP control. As a result, people with hypertension who are both controlled and uncontrolled by office measurements make up the resistant hypertensive population [1].

In its definition of resistant hypertension, the American Heart Association (AHA) makes no attempt to differentiate between resistant and pseudo-resistant hypertension. The term "pseudo-resistant hypertension" refers to individuals who do not actually have true resistant hypertension but do have elevated office blood pressures as a result of white-coat hypertension, improper BP measurement, or medication non-adherence. Epidemiological studies used the term "apparently resistant hypertension" when referring to the group of patients who were taking three antihypertensive medications and had an office BP greater than 140/90 mmHg. This was done to make it clear that pseudo-resistance had not been ruled out. The distinction between true and apparent resistance can be made after pseudo-resistance has been excluded through proper office BP measurement technique, 24-hour ambulatory BP monitoring, and confirmation of medication adherence [2]. As a result, true resistant hypertension is defined as a properly measured office BP greater than 140/90 mmHg and a mean ambulatory BP greater than 130/80 mmHg over the course of 24 hours in a patient who has been confirmed to be taking three antihypertensive medications. Excluding participants with pseudo-resistant hypertension from the test population makes it difficult to determine the prevalence of true resistant hypertension.

A prospective cohort study in a large hypertensive population with forced titration up to full doses of three different classes of antihypertensive medications, including a diuretic, would be ideal for estimating the prevalence of true resistant hypertension. Additionally, 24-hour ambulatory BP monitoring, standardized BP measurement, and an established method for establishing adequate medication adherence (such as electronic pill bottle monitoring, pill counts, or toxicology) would need to be used to rule out pseudo-resistant hypertension. This study has not yet been conducted, but the prevalence of resistant hypertension is estimated from: 1) BP control data from population studies; 2) outcome-based clinical trial subpopulations; 3) retrospective analyses of registry data; and 4) population studies that specifically identify resistant hypertension. Indirect estimates of the prevalence of resistant hypertension are provided by population studies on the prevalence, treatment, and control of hypertension [3]. The number of patients taking fewer than three antihypertensive medications and overall BP control rates are frequently reported in these studies. One can estimate the proportion of patients uncontrolled on fewer than three medications and the prevalence of apparent resistant hypertension by assuming comparable control rates among the population taking at least three medications [4].

1856 of the 8299 patients in a 2009 Italian study who were receiving treatment for hypertension from a general practitioner received at least three medications. Although the most common two-drug combination was an angiotensin-converting enzyme inhibitor and a diuretic, the percentage of diuretics used and optimal medication dosing were not reported. The European Society of Hypertension and European Society of Cardiology guidelines stated that the group taking fewer than three medications had a BP control rate of 22.3%. In this treated hypertensive populace, 17.4% are uncontrolled on three prescriptions [5]. When interpreting the prevalence rates from outcome-based studies like Allhat, Life, Invest, and Accomplish, for instance, there is uncertainty. It is difficult to determine whether more or fewer people with resistant hypertension were included in these studies. It's possible that including people with resistant hypertension was more likely if participants

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were chosen specifically based on their cardiovascular risk. Additionally, antihypertensive titration protocols were not developed to maximize three or four drug regimens. By deteriorating BP control, a non-optimal multi-drug regimen would falsely raise the prevalence of resistant hypertension. When compared to hydrochlorothiazide plus benazepril, ACCOMPLISH had the highest control rate of the four outcome trials when it added spironolactone, alpha-blockers, or beta-blockers to amlodipine plus benazepril. As a result, only 8.4% of those treated for hypertension were uncontrolled on fewer than three medications.

White-coat hypertension was present in 35.7% of the uncontrolled resistant population, according to some studies, which provide insight into the degree of underestimation or overestimation associated with each cause. According to pharmacy refill rates, Daugherty discovered that 12.4% of the uncontrolled resistant population was not adherent to their medical regimens. According to data, the prevalence of resistant hypertension rises by up to 12.1% with an increase in the number of antihypertensive medications. In addition, urine toxicology revealed that 53% of uncontrolled individuals were nonadherent in a study aimed at determining the degree of medication adherence among people with resistant hypertension. 30% of nonadherents did not take any antihypertensive medication. These studies, taken together, suggest that white-coat hypertension or pseudo-resistant hypertension caused by nonadherence probably account for half of all uncontrolled resistant hypertensive patients. As a result, the estimated prevalence of true resistant hypertension among treated and all hypertensive individuals is 4.0% and 5.0%, respectively.

Conclusion

True and apparent hypertension resistance are complex, multifactorial conditions that significantly impact patient outcomes and pose challenges to clinical management. Distinguishing between the two is crucial, as true resistance requires intensive medical interventions and often involves secondary causes, while apparent resistance can often be resolved by addressing behavioral, measurement, or therapeutic issues. The epidemiology of hypertension resistance underscores its widespread prevalence, emphasizing the need for heightened awareness and systematic approaches to diagnosis. The clinical implications are profound, with true resistant hypertension correlating strongly with adverse cardiovascular and renal outcomes. Addressing apparent

resistance by ensuring accurate blood pressure measurement, improving medication adherence, and ruling out secondary factors can significantly enhance the management of hypertensive patients and reduce unnecessary treatment escalations. Future research must focus on refining diagnostic criteria, improving patient stratification, and exploring innovative therapeutic options for resistant hypertension. Integrating advanced technologies, such as home blood pressure monitoring and precision medicine approaches, can further aid in distinguishing between true and apparent resistance, ultimately enhancing patient care. By adopting a comprehensive and individualized approach, healthcare providers can better address the challenges posed by resistant hypertension and improve both short-term control and long-term outcomes for affected individuals.

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